REMARKS

Claims 12-26 have been cancelled.

Claim 1 has been amended to recite "[a] recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism, thereby is capable of producing carotenoids in an enhanced level relative to the host microorganism, characterized in that it contains an antisense polynucleotide against a nucleic acid molecule selected from the group consisting of:

(a) nucleic acid molecules encoding the polypeptide in SEQ ID NO:3;

(b) nucleic acid molecules comprising the sequence in SEQ ID NO:2;

(c) nucleic acid molecules whose nucleotide sequence is degenerate as a result of the genetic code to a nucleotide sequence of (a) or (b);

(e) nucleic acid molecules encoding a polypeptide derived from the polypeptide whose sequence has an identity of 51.3 % or more to the amino acid sequence of the polypeptide encoded by a nucleic acid molecule of (a) or (b);

(g) nucleic acid molecules-comprising a polynucleotide having a sequence of a nucleic acid molecule amplified from a Phaffia nucleic acid library using the primers depicted in SEQ ID NO:4, 5, and 6;

(j) nucleic acid molecules encoding a polypeptide having squalene synthase activity, wherein said polypeptide is recognized by antibodies that have been raised against a polypeptide encoded by a nucleic acid molecule of any one of (a), (b), (c) and (g);

(k) nucleic acid molecules obtainable by screening an appropriate library under high stringency conditions with a probe having the sequence of the nucleic

acid molecule of any one of (a), (b), (c), (e), (g) and (j), and encoding a polypeptide having squalene synthase activity, wherein the high stringency conditions include hybridizing in 6xSSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA, 50% formamide overnight at 42° C and washing once in 2xSSC, 0.5% SDS at room temperature for 15 minutes followed by a second wash in 0.1xSSC, 0.5% SDS at room temperature for 15 minutes." Support for this amendment is found in the specification at, for example, page 6, lines 16-27; page 19, lines 11-14; in Examples 1-9; and in original claims 14, 21, 22, 25, and 26. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8th ed. Rev. 5, August 2006, pp. 600-92 and 600-84).

Claim 2 has been amended to recite "[a] recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism, thereby is capable of producing carotenoids in an enhanced level relative to the host microorganism, characterized in that it contains an antisense polynucleotide against a nucleic acid molecule selected from the group consisting of:

(m) nucleic acid molecules comprising the nucleotide sequence as depicted in SEQ ID NO:1;

(n) nucleic acid molecules whose nucleotide sequence is degenerate as a result of the genetic code to a nucleotide sequence of (m);

(p) nucleic acid molecules encoding a polypeptide derived from the polypeptide whose sequence has an identity of 51.3 % or more to the amino acid sequence of the polypeptide encoded by a nucleic acid molecule of (m);

(q) nucleic acid molecules comprising a fragment encoded by a nucleic acid molecule of any one of (m), (n) or (p) and having squalene synthase activity;

(r) nucleic acid molecules comprising a polynucleotide having a sequence of a nucleic acid molecule amplified from a Phaffia nucleic acid library using the primers depicted in SEQ ID NO:4, 5, and 6;

(s) nucleic acid molecules encoding a polypeptide having squalene synthase activity, wherein said polypeptide is a fragment of a polypeptide encoded by any one of (m), (n), (p), (q) and (r);

(t) nucleic acid molecules comprising at least 15 nucleotides of a polynucleotide of (m);

(u) nucleic acid molecules encoding a polypeptide having squalene synthase activity, wherein said polypeptide is recognized by antibodies that have been raised against a polypeptide encoded by a nucleic acid molecule of any one of (m), (n), (p), (q), (r) and (s);

(v) nucleic acid molecules obtainable by screening an appropriate library under high stringency conditions with a probe having the sequence of the nucleic acid molecule of any one of (m), (n), (p), (q), (r), (s), (t) and (u), and encoding a polypeptide having squalene synthase activity, wherein the high stringency conditions include hybridizing in 6xSSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA, 50% formamide overnight at 42° C and washing once in 2xSSC, 0.5% SDS at room temperature for 15 minutes followed by a second wash in 0.1xSSC, 0.5% SDS at room temperature for 15 minutes;

(w) nucleic acid molecules whose complementary strand hybridizes under high stringency conditions with a nucleic acid molecule of any one of (m), (n), (p), ((l), (r), (s), (t), (u), (v), and encoding a polypeptide having squalene synthase activity, wherein the high stringency conditions include hybridizing in 6xSSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA, 50% formamide overnight at 42° C and washing once in 2xSSC, 0.5% SDS at room temperature for 15 minutes followed by a second wash in 0.1xSSC, 0.5% SDS at room temperature for 15 minutes." Support for this amendment is found in the specification at, for example, page 6, lines 16-27; page 19, lines 11-14; in Examples 1-9; and in original claims 14, 21, 22, 25, and 26. (*Id.*).

Claims 3 and 4 have been amended to recite a "recombinant microorganism" polynucleotide instead of an "isolated polynucleotide." Claim 4 has also been amended to recite "isolated from" instead of "derived from." These amendments do not change the scope of the claims in any way.

Claims 8, 10, and 11 have been amended to recite "recombinant microorganism" instead of "recombinant organism." Claims 8 and 9 have been amended to recite "host microorganism" instead of "host organism." Support for this amendment is found in the specification at, for example, page 12, lines 11-22; page 25, lines 13-18; in Examples 1-9; and in original claim 26. (*See id.*).

Claim 9 has been amended to remove "baculovirus."

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

New claims 27-40 have been added. Support for these new claims is found in the specification at, for example, page 6, lines 1-27; page 10, lines 18-21; page

19, lines 11-14; in Examples 1-9; and in original claims 1, 2, 4-11, 14, 21, 22, 25, and 26. *Id.*

Objections:

The Examiner objected to claims 1 and 2 because of typographical errors. The Examiner asserted that the recitation "undkr" should be "under," and the recitation "InISEQ" should instead state "in SEQ." (Paper No. 20061011 at 2).

With a view towards furthering prosecution, claims 1 and 2 have been amended, as suggested by the Examine. In view of the foregoing amendments, the objection of claims 1 and 2 is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. § 101:

Claims 8 and 10 were rejected under 35 U.S.C. § 101. In making the rejection, the Examiner asserted that claims 8 and 10 recite "an organism encompassing transformed humans ..., which is non-statutory subject matter." (*Id.* at 3).

With a view towards furthering prosecution, claims 8 and 10 have been amended to recite a "recombinant microorganism." In view of the foregoing amendment, the rejection of claims 8 and 10 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Indefiniteness Rejections:

Claims 1-11 were rejected under 35 USC § 112, second paragraph. (*Id.* at 4). In making this rejection, the Examiner asserted that claims 1 and 2 recite

"'stringent conditions', [and] the specification does not define what conditions constitute 'stringent'." (*Id.*).

Initially, we respectfully note that the Examiner's conclusion that the specification does not define "what conditions constitute stringent" is in error. High stringency hybridization and wash conditions are clearly disclosed at, *e.g.*, page 6, lines 17-20 of the specification:

> High Stringent Hybridization: 6xSSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA, 50% formamide, incubate overnight with gentle rocking at 42° C.
> High Stringent Wash: 1 wash in 2xSSC, 0.5% SDS at room temperature for 15 minutes, followed by another wash in 0.1xSSC, 0.5% SDS at room temperature for 15 minutes.

Based on this disclosure and with a view towards furthering prosecution, claims 1 and 2 have been amended to recite these high stringency hybridization and wash conditions. In view of the foregoing, the rejection of claims 1 and 2 (and dependent claims 3-11) is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 1 was also rejected under 35 USC § 112, second paragraph. (*Id.*). In making the rejection, the Examiner observed that claim 1(b) recites "comprising the coding sequence as depicted in SEQ ID NO:2." The Examiner then asserted that it "is unclear whether it comprises all of SEQ ID NO:2 or only part of it and if so what part." (*Id.*).

With a view towards furthering prosecution, claim 1 has been amended to recite "nucleic acid molecules comprising the sequence in SEQ ID NO:2." In view of the

foregoing, this rejection of claim 1 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 1 was also rejected under 35 USC § 112, second paragraph. (*Id.*). In making the rejection, the Examiner asserted that claim 1(a) recites the "mature form of SEQ ID NO:3." The Examiner then asserted that "the specification does not indicate what portion of SEQ ID NO:3 this corresponds to." (*Id.*).

With a view towards furthering prosecution, claim 1 has been amended to recite "nucleic acid molecules encoding the polypeptide in SEQ ID NO:3." In view of the foregoing, the rejection of claim 1 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 2 was also rejected under 35 USC § 112, second paragraph. (*Id.*). In making the rejection, the Examiner asserted that in part (t) of claim 2, "(a) has no antecedent basis." (*Id.*).

With a view towards furthering prosecution, claim 2 been amended to remove the rejected "or (a)" language. In view of the foregoing, the rejection of claim 2 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 4 was also rejected under 35 USC § 112, second paragraph. (*Id.*). In making the rejection, the Examiner asserted that in claim 4 the recitation "derived from" "is "unclear." (*Id.*).

With a view towards furthering prosecution, claim 4 been amended to recite "isolated from" instead of "derived from." In view of the foregoing, the rejection of claim 4 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 9 was also rejected under 35 USC § 112, second paragraph. (*Id.*). In making the rejection, the Examiner observed that claim 9 recites "baculovirus" as an organism. The Examiner then asserted that "baculovirus is not an organism, it is [a] virus." (*Id.*).

With a view towards furthering prosecution, claim 9 has been amended to remove the rejected to language. In view of the foregoing, the rejection of claim 9 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

§112, First Paragraph Rejections:

1. Written Description

Claims 1-11 have been rejected under 35 U.S.C. §112, first paragraph. (Paper No. 20061011 at 5-6). In making the rejection, the Examiner asserted that claims 1-11 "contain[] subject matter, which was not described in specification ...." (*Id.*). The Examiner further asserted that "[t]he specification discloses only a single species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus." (*Id.*). The Examiner also asserted that "[t]hese claims are directed to a genus of DNA molecules with either SEQ ID NO: 2 and any variant of [sic] thereof or any DNA which will hybridize to SEQ ID NO: 2 under any conditions or any DNA amplified [from a] Phaffia nucleic acid with primers of SEQ ID NOS: 4-6 or DNA having the limitations of encoding a protein having the sequence of amino acid SEQ ID NO: 3 and any protein variant of thereof having upto [sic] 51.3% sequence identity with SEQ ID NO: 3 or any DNA encoding any SQS polypeptide recognized by any antibody against any variant of SEQ ID NO: 3 or any fragment thereof." (*Id.* at 5). The Examiner then concluded that "one skilled in the art

cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed." (*Id.* at 6).

Initially, we note that there is a ***strong presumption*** that an adequate written description of the claimed invention is present in an application as filed. *See In re Werthheim*, 191 USPQ 90, 97 (CCPA 1976); and MPEP §2163(II)(A). Further, an applicant may show possession of the claimed invention by describing it using descriptive means such as, for example, words, structures, figures, diagrams and formulas. *See* MPEP §2163(I). Moreover, a proper written description analysis requires an analysis of the understanding of an ordinarily skilled artisan at the time of the invention. *See* MPEP § 2163(II)(A)(2); *see also Wang Labs. v. Toshiba Corp.*, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993).

With a view towards furthering prosecution, independent claims 1 and 2 have been amended as set forth above.

Specifically, claims 1 and 2, as amended, recite, *inter alia*, ***specific nucleic acid molecules***, *e.g.*, SEQ ID NO: 2 and nucleic acid molecules encoding the polypeptide in SEQ ID NO: 3. In addition, claims 1 and 2, as amended, recite specific high stringency conditions. Moreover, claims 1 and 2, as amended, recite ***(1)*** a "recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism," ***(2)*** the recombinant microorganism "is capable of producing carotenoids in an enhanced level relative to the host microorganism," and ***(3)*** the recombinant microorganism "contains an antisense polynucleotide against a nucleic acid molecule selected from the group consisting of: ...." As amended, the nucleic acid molecules in claims 1 and 2 are specifically tied to recited functions. Support for these

amendments is found virtually *in haec verba* in the specification. (*See, e.g.*, page 6, lines 16-27; page 19, lines 11-14; in Examples 1-9; and in original claims 14, 21, 22, 25, and 26). Thus, there is a built-in tie between the recited structures and functions. Moreover, the specification exemplifies a number of ways to confirm the recited functions, namely that the gene expression of squalene synthase is reduced compared to a host microorganism and that the recombinant microorganism is capable of producing carotenoids in an enhanced level relative to the host microorganism. (*See, e.g.*, page 18, lines 1-16; page 21, line 9 to page 24, line 30; and Examples 1-9). Nothing more need be provided. Thus, in view of these amendments, it is respectfully submitted that the claims fully satisfy the written description requirement.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

2. Enablement

Claims 1-11 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20061011 at 6). In making the rejection, the Examiner acknowledged that the specification is "enabling for the DNA of SEQ ID NO: 2 or a DNA encoding polypeptide of SEQ ID NO: 3 having squalene synthase activity, ..." (*Id.*)

The Examiner, however, asserted that the specification "does not reasonably provide enablement for any DNA molecules of SEQ ID NO: 2 or any variant thereof or any DNA which will hybridize to SEQ ID NO: 2 under any stringent condition or any DNA made by amplifying Phaffia nucleic acid with primers of SEQ ID NOS: 4-6 or DNA having the limitations of encoding a protein having the sequence of amino acid SEQ ID NO: 3 and any protein variant [ ] thereof having upto 51.3% sequence identity

with SEQ ID NO: 3 or any DNA encoding any SQS polypeptide recognized by any antibody against any variant of SEQ ID NO 3 or any fragment thereof." (*Id.*).

Initially, we note it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry this burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370. It is well established that claims must be separately analyzed. *Ex parte Jochim*, 11 USPQ2d 561 (BPAI 1988).

With a view towards furthering prosecution, however, independent claims 1 and 2 have been amended as discussed above.

As amended, claims 1 and 2 recite, *inter alia*, ***specific nucleic acid molecules***, *e.g.*, SEQ ID NO: 2 and nucleic acid molecules encoding the polypeptide in SEQ ID NO: 3, which the Examiner concedes are enabled. (Paper No. 20061011 at 6). Claims 1 and 2, as amended, also recite specific high stringency hybridization conditions. Moreover, claims 1 and 2, as amended, recite ***(1)*** a "recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism," ***(2)*** the recombinant microorganism "is capable of producing carotenoids in an enhanced level relative to the host microorganism," and ***(3)*** the recombinant microorganism "contains an antisense polynucleotide against a nucleic acid molecule selected from the group consisting of: ...." The nucleic acid molecules in amended claims 1 and 2 are specifically tied to the recited functions, namely that the gene expression of squalene synthase is reduced compared to a host microorganism

and that the recombinant microorganism is capable of producing carotenoids in an enhanced level relative to the host microorganism. With these amendments, it is respectfully submitted that the Examiner's concerns regarding the scope of the claims, *i.e.*, "***any*** DNA molecules of SEQ ID NO: 2 or ***any variant*** thereof or ***any*** DNA which will hybridize to SEQ ID NO: 2 ***under any stringent condition*** or ***any*** DNA made by amplifying Phaffia nucleic acid with primers of SEQ ID NOS: 4-6 ... and ***any protein variant*** or ***any*** DNA encoding ***any*** SQS polypeptide ...," is rendered moot. (Paper No. 20061011 at 6) (emphasis added).

Moreover, as is well accepted, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. In addition, "a patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01 (8th ed. Rev. 5, August 2006, p. 2100-187) *citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In this regard, we note that the specification provides ample disclosure sufficient to inform a skilled artisan that the Applicants enabled the currently claimed polynucleotides. For example, the specification discloses 9 examples that provide sufficient instruction to one skilled in the art on how to make and use the currently claimed polynucleotides. The specification also discloses methods for identifying polynucleotides that encode polypeptides that have the functions recited in amended

claims 1 and 2. (*See, e.g.*, page 6, lines 16-27; page 18, lines 1-16; page 21, line 9 to page 24, line 30; and Examples 1-9). Thus, identifying nucleic acid molecules recited by amended claims 1 and 2 is a matter of applying the disclosure in the specification of how to make such molecules and running them through the disclosed functional screening assays. It is respectfully submitted that such activity is not undue experimentation.

In particular, the specification discloses that an "expressed SQS gene can be verified for its activity such as by enzyme assay method" and then gives an example of such a method that is "used for the determination of squalene synthase activity." (Page 18, lines 1-16). The specification also explains multiple strategies to decrease gene expression. One strategy disclosed in the specification is the antisense method. "This method is frequently applied to decrease the gene expression even when teleomorphic organisms such as *P. rhodozyma* are used as host organisms, to which the mutation and gene disruption method is usually difficult to be applied. The anti-sense method is a method to decrease an expression of [a] gene of interest by introducing an artificial gene fragment, whose sequence is complementary to [a] cDNA fragment of the gene of interest." (See page 21, line 9 to page 24, line 30). Also, Examples 1-9 disclose detailed isolation, cloning, sequencing, and hybridization methods and techniques for the squalene synthase (SQS) gene. In particular, Examples 7, 8, and 9 disclose how to make and use vectors containing antisense constructs against polynucleotides that encode SQS polypeptides, transformation of *P. rhodozyma* with the SQS-antisense vector, and characterization of antisense SQS recombinant of *P. rhodozyma*.

For the reasons set forth above, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

Claims 8 and 9 have also been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Paper No. 20061011 at 8-9).

In making the rejection, the Examiner asserted that the specification "does not reasonably provide enablement for host cells within a multicellular organism that have been transformed with the synthetic nucleic acid." (*Id.* at 9). The Examiner further asserted that "[c]laim[s] 8-9 are so broad as to encompass host cells transformed with specific nucleic acids, including cells in *in vitro* culture as well as cells within any multicellular organism." (*Id.*). The Examiner, however, acknowledged that the specification is "enabling for an isolated host cell transformed with the synthetic nucleic acid." (*Id.* at 8-9).

With a view towards furthering prosecution, claims 8 and 9 have been amended to recite "host microorganism" instead of "host organism." In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(b):

Claims 1-3 and 5-11 were rejected under 35 USC § 102(b) as anticipated by Robinson, G.W. *et al., "Conservation Between Human and Fungal Squalene Synthetases: Similarities in Structure, Function, and Regulation,"* Molecular and Cellular Biology, vol. 13, no. 5, pp. 2706-2717 (1993) ("Robinson"). (Paper No. 20061011 at 10-11).

For the reasons set forth below, the rejection, has been rendered moot.

Robinson discloses that "[s]qualene synthetase (farnesyl diphosphate:farnesyl diphosphate farnesyltransferase; EC 2.5.1.21) is thought to represent a major control point of isoprene and sterol biosynthesis in eukaryotes." (Abstract). Robinson also discloses "structural and functional conservation between [ ] enzymes from humans, a budding yeast (*Saccharomyces cerevisiae*), and a fission yeast (*Schizosaccharomyces pombe*). The amino acid sequences of the human and *S. pombe* proteins deduced from cloned cDNAs were compared to those of the known *S. cerevisiae* protein." (*Id.*). Furthermore, "[a] comparison of amino acid sequences of the three squalene synthetases is shown in Fig. 5. Conservation is especially poor at the proteins' amino and carboxyl termini. Overall, there is ***only 36% amino acid identity*** and approximately 57% similarity in any pairwise comparison of the three proteins." (Page 2710, left column, second paragraph, and Fig. 5) (emphasis added).

In making the rejection, the Examiner asserted that Robinson "teaches nucleotide[s] encoding squalene synthase (SQS) of gene from *S. pombe*, vector and transformed cell (E. coli) which is 51.3% sequence identity with applicant gene encoding SQS of SEQ ID NO: 3." (Paper No. 20061011 at 11). The Examiner further asserted that in Robinson the "polynucleotide encoding *S. pombe* SQS will hybridize with any fragment of applicant[s'] nucleic acid encoding SEQ ID NO: 3 under low stringent condition[s]." (*Id.*).

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single ***prior art reference*** and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA

1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir 1984). "Moreover, it is incumbent upon the Examiner to ***identify wherein each and every facet*** of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads. *Chiong v. Roland*, 17 USPQ2d 1541, 1543 (BPAI 1990). This the Examiner has not done.

In making the rejection, the Examiner never asserted that Robinson discloses each and every element recited in the claims. However, it is the claims that define what the applicant deems as his invention and ***it is the claims which are examined and rejected***, if appropriate. *See* 37 CFR § 1.104(c). In the Office Action, the Examiner only presented two cryptic sentences, which allegedly anticipate claims 1-3 and 5-11. The Examiner provided no citations to Robinson where these asserted "teachings" can be found in the reference. That, however, was the Examiner's burden. Thus, even if the Examiner's cryptic characterization of Robinson is accepted as correct, which it is not, the Examiner has not demonstrated that Robinson discloses what is claimed. This, however, is not the stuff of a §102 rejection. Having failed to analyze each and every element recited in the claims, the rejection is both legally and factually deficient. For this reason alone, the rejection should be withdrawn.

As noted above with respect to the §112 rejections, claims 1 and 2 have been amended to recite "***[a] recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism, thereby is capable of producing carotenoids in an enhanced level relative to the host***

microorganism, characterized in that it contains an antisense polynucleotide against a nucleic acid molecule selected from the group consisting of: ...." Claims 1 and 2 have also been amended to recite, *inter alia*, high stringency conditions.

As discussed above, Robinson, on page 2710, left column, second paragraph, discloses that there is only 36% amino acid identity in any pairwise comparison of the three proteins examined. This does not disclose or suggest a "***recombinant microorganism whose gene expression of squalene synthase is reduced compared to a host microorganism***" as recited in currently amended claims 1 and 2. Further, Robinson does not discloses or suggest "***producing carotenoids in an enhanced level relative to the host microorganism, characterized in that it contains an antisense polynucleotide against a nucleic acid molecule ...***" *as* recited in currently amended claims 1 and 2. Nor does Robinson disclose (1) SEQ ID NO: 2, (2) SEQ ID NO:3, or (3) polynucleotides that hybridize under high stringency conditions to any of the recited polynucleotides, or any other polynucleotide/polypeptide sequence recited in either claim 1 or claim 2. For this further reason, the rejection has been rendered moot and should be withdrawn.

The rejection is also devoid of any discussion of the dependent claims. Accordingly, the record is devoid of any evidence that the Examiner individually considered the dependent claims. It is axiomatic, however, that a dependent claim is not *per se* unpatentable by a document that allegedly makes unpatentable the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art,***

exactly as if it were presented as one independent claim." MPEP § 608.01(n) (8th ed., Rev. 5, Aug. 2006, pp. 600-91). This the Examiner has not done. Accordingly, the rejection is both factually and legally deficient as to the dependent claims. For this additional reason, the rejection should be withdrawn as to the dependent claims.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the objections and rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on April 17, 2007.

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